PATENT SPECIFICATION (11) 1242096

1242096

NO DRAWINGS

(21) Application No. 60855/68 (22) Filed 20 Dec. 1968

(23) Complete Specification filed 3 Dec. 1969

(45) Complete Specification published 11 Aug. 1971

(51) International Classification C 07 d 21/00 99/04

(52) Index at acceptance

C2C 181—270—283 1E5K4 1E6K4 1E7B1 1E7E1 1E7N5 1G5B 1G6B4 1G6B6 200 213 214 246 247 253 25Y 29X 29Y 30Y 313 31Y 323 32Y 337 360 363 364 36Y 3A12A4B 3A12B1 3A12C5 3A13A3A4 3A13A3B3 3A13A3F3 3A13C10F 3A13C10H

ERRATA

SPECIFICATION No. 1,242,096

Page 1, Heading, (72) Inventors *for* "DESCHAMPS" *read* "DESCAMPS"

Page 3, lines 78 and 86, *for* "parental" *read* "parenteral"

Page 3, line 94, *for* "IV" *read* "VI"

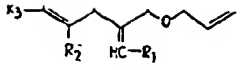
Page 4, line 61, *for* "oexpine" *read* "oxepine"

Page 4, line 85, *for* "Perparation" *read* "Preparation"

Page 6, line 5, *for* "indinopropylidene" *read* "idinopropylidene"

Page 6, line 34, *for* "147" *read* "247"

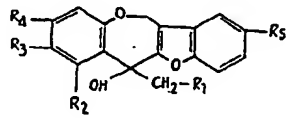
THE PATENT OFFICE
21st February 1972



I

wherein R_1 represents β-dimethylaminoethyl, β - dimethylaminoisopropyl, β - piperidinoethyl, β - (4 - methylpiperazino) - ethyl, (1 - methyl - 2 - piperidyl) - methyl or 1 - methyl - 3 - piperidyl; R_2 represents hydrogen or methyl; R_3 represents hydrogen, chlorine, methyl or methoxy; R_4 represents hydrogen or methyl and R_5 represents hydrogen, chlorine or methoxy. The compounds of formula I form acid addition salts with inorganic and organic acids and hence the invention includes within its scope pharmaceutically acceptable acid addition salts of the compounds of formula I.

The compounds of formula I may be prepared by reacting in a suitable ether, for example tetrahydrofuran, diethyl ether, propyl ether, isopropyl ether or butyl ether, a 6 - [illegible] wherein Hal represents chlorine or bromine and R_1 has the same meaning as in formula I, to form a magnesium organic derivative which is hydrolysed to form a 6 - hydroxy derivative represented by the general formula:



III

wherein R_1, R_2, R_3, R_4 and R_5 have the same meanings as in formula I.

The compounds of formula III are then reacted with a dehydrating agent such as a strong acid, for example sulphuric acid, hydrochloric acid, phosphoric acid or *p* - toluene - sulphonic acid, or an inorganic or or-

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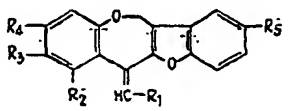
(72) Inventors FERNAND BINON and MARCEL DESCHAMPS

(54) BENZOBENZOFURANOOXEPINE COMPOUNDS AND PROCESS FOR PREPARING THE SAME

(71) We, LABAZ, formerly known as Laboratoires Labaz, of 39, avenue Pierre 1 er de Serbie, Paris 8e, France a French body Corporate, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

This invention relates to novel benzo[b]-benzofurano[2, 3-e]oxepine derivatives and to a process for preparing the same.

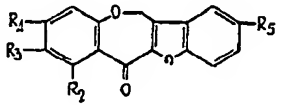
The benzo[b]benzofurano[2, 3-e]oxepine derivatives with which the invention is concerned are represented by the general formula:



I

wherein R_1 represents β-dimethylaminoethyl, β - dimethylaminoisopropyl, β - piperidinoethyl, β - (4 - methylpiperazino) - ethyl, (1 - methyl - 2 - piperidyl) - methyl or 1 - methyl - 3 - piperidyl; R_2 represents hydrogen or methyl; R_3 represents hydrogen, chlorine, methyl or methoxy; R_4 represents hydrogen or methyl and R_5 represents hydrogen, chlorine or methoxy. The compounds of formula I form acid addition salts with inorganic and organic acids and hence the invention includes within its scope pharmaceutically acceptable acid addition salts of the compounds of formula I.

The compounds of formula I may be prepared by reacting in a suitable ether, for example tetrahydrofuran, diethyl ether, propyl ether, isopropyl ether or butyl ether, a 6 - oxo - benzo[b]benzofurano[2, 3 - e]oxepine of the general formula:

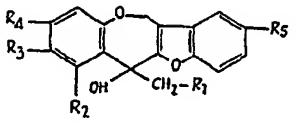


II

in which R_2, R_3, R_4 and R_5 have the same meanings as in formula I, with a halogenomagnesium organic compound of the general formula

$$HalMg—CH_2—R_1$$

wherein Hal represents chlorine or bromine and R_1 has the same meaning as in formula I, to form a magnesium organic derivative which is hydrolysed to form a 6 - hydroxy derivative represented by the general formula:



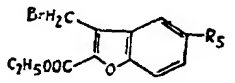
III

wherein R_1, R_2, R_3, R_4 and R_5 have the same meanings as in formula I.

The compounds of formula III are then reacted with a dehydrating agent such as a strong acid, for example sulphuric acid, hydrochloric acid, phosphoric acid or p - toluene - sulphonic acid, or an inorganic or or-

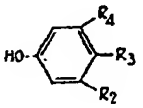
ganic acid chloride, for example thionyl chloride, acetyl chloride or tosyl chloride, to form the corresponding 6 - methylidene derivative (i.e. the required compound of formula I), which may then be reacted with an appropriate organic or inorganic acid to provide a pharmaceutically acceptable acid addition salt of the compound of formula I.

The starting compound represented by formula II may be prepared by reacting an ethyl 3 - bromoethyl-coumarilate represented by the general formula:



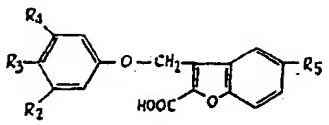
IV

wherein R_5 has the same meaning as in formula I, with a phenol of the general formula:



V

wherein R_2, R_3 and R_4 have the same meanings as in formula I, to form the corresponding ethyl 3 - phenoxymethyl - coumarilate which, after saponification with, for example, a hydroalcoholic solution of potassium hydroxide, yields a 3 - phenoxymethyl - coumarilic acid represented by the general formula:



VI

wherein R_2, R_3, R_4 and R_5 have the same meanings as in formula I.

The compound of formula VI may then be converted to its corresponding acid chloride by means of, for example, thionyl chloride and directly cyclised, for example in an appropriate solvent such as dichloroethane at a temperature below 20°C. and in the presence of stannic chloride, to form the corresponding 6 - oxo - benzo[b]benzofurano[2, 3 - e]-oxepine represented by formula II.

The compound of formula IV in which R_4 represents hydrogen is a known compound. Those in which R_4 represents chlorine or methoxy may be prepared by the method described in Helv. Chim. Acta, *31*, 78, 1948, from ethyl 3 - methyl - coumarilate.

The compounds of formula V are also known compounds.

The compounds of the present invention have been unexpectedly found to possess valuable pharmacological activity. It has been observed that compounds of the invention are antagonistic to serotonin and histamine which are considered as playing a biochemical role in the generation and maintainance of cephalalgia of various origins and, in particular, migraine. This indicates that compounds of the invention possess the necessary biochemical properties to render them valuable agents in the treatment of such pathological conditions.

In addition to this fairly specific activity, pharmacological trials have shown that compounds of the invention possess antalgic properties, probably due in part to an action on the central nervous system, which render them useful in the treatment of a broader variety of pain. Animals which had received compounds of the invention showed markedly diminished reaction to painful stimulation as compared with untreated animals.

Finally, it has been observed that compounds of the invention possess an antiemetic activity which constitutes a valuable adjunct to the antalgic properties already mentioned.

Compounds which have proved to be particularly useful in this field are 6 - (3 - *dimethylaminopropylidene*) - benzo[b]benzofurano[2, 3 - e]oxepine (in the form of its fumarate)and 6 - (3 - piperidinopropylidene) - benzo[b]benzofurano[2, 3 - e]oxepine (in the form of its oxalate).

Pharmacological tests were performed with these two compounds to determine their inhibitory effects on serotonin and histamine. For the purpose of these tests the compound 6 - (3 - *dimethylaminopropylidene*) - benzo-[b]benzofurano[2, 3 - e]oxepine fumarate is hereinafter designated as Compound I, while the compound 6 - (3 - piperidinopropylidene) - benzo[b]benzofurano[2, 3 - e]oxepine oxalate is hereinafter designated as Compound II.

To provide a means of comparison with the prior art, the same tests were performed with a well-known substance recognized as possessing anti-serotonin and anti histamine activity and which is particularly useful in the treatment of conditions characterised by migraine. This substance was 10 - [(2 - dimethylamino)propyl] - N, N - dimethylphenothiazine - 2 - sulphonamide (hereinafter referred to as Compound III).

For the anti-serotonin test, the technique of Gaddum and Hameed was employed whereby an isolated uterus of rat was placed in a 50 ml. bath of Locke's Solution and different doses of serotonin applied in order to discover the dose at which a reasonably intense spasm of the uterus was obtained.

Subsequent trials were then made with each of the compounds to be tested in order to discover what concentration of each compound was required in the bath to reduce by 50% the spasm provoked by the previously determined dose of serotonin (AD_{50}). The results of the test were based on two factors, namely the intensity and the duration of the anti-spasmodic effect.

This test showed that both Compounds I and II possess an anti-serotonin activity which is approximately one-and-a-half times that of Compound III. Furthermore, the duration of the action of Compounds I and II was found to be twice as long as that of Compound III (two hours as against one hour).

For the anti-histamine test, McKeon's technique was used *in vivo* on the guinea-pig. According to this technique, intravenous doses of histamine were administered to guinea-pigs until the dose required to kill an animal within three minutes was determined. Subsequently, this dose was administered intravenously to other guinea-pigs simultaneously with varying doses of the compound to be tested in order to find out how much of the latter was required to prevent death occurring over a period of six minutes in 50% of the animals (AD_{50}).

It was found that the AD_{50} of Compound I was approximately one third of that of Compound III while the AD_{50} of Compound II was five times the value of Compound III. This test showed that both Compounds I and II, and particularly Compound I, are active anti-histaminics.

Finally, antalgic tests of a purely physiological nature were performed according to the technique of Lund Nilsen. For these tests, male mice were used and two electrodes were inserted subcutaneously into their tails near the extremity. The required voltage to produce a painful reaction was determined for each animal. Varying doses of the compound to be tested were then given by intragastric intubation to the mice until the average dose required to suppress the painful reaction in 50% of the animals was determined (AD_{50}).

It was found that the AD_{50} for compound I was 12 mg/kg of body-weight and for Compound II 75 mg/kg, while that for Compound III was 80 mg/kg. These results show that Compound I exerts an antalgic effect which is approximately seven times that of Compound III while Compound II is slightly superior to Compound III.

Since the compounds of formula I are normally oily liquids, it will be appreciated that for therapeutic use the pharmaceutically acceptable acid addition salts of the compounds of formula I were advantageously used rather than the free bases.

It will be appreciated that for therapeutic use the compounds of the invention will normally be administered in the form of a pharmaceutical composition comprising as an essential active ingredient a compound of formula I, in association with a pharmaceutical carrier therefor. The carrier may be a solid or liquid diluent or excipient of the kind normally employed in the production of medicaments ready for use, for example lactose, potato starch, talc, magnesium stearate, gelatine, sodium chloride or distilled water.

The composition may be made up in a form suitable for the desired mode of administration, which may be by the oral, rectal or parental route. Advantageously for clinical use, the composition is made up in a dosage unit form adapted for the desired mode of administration. The dosage unit may be, for example, a tablet, pill, packaged powder, capsule, syrup or drops for oral administration or suppository or a sterile solution packaged in a sealed container, such as an amouple for parental administration. The amount of active ingredient in each dosage unit will be such that one or more units are required for each therapeutic administration.

The following Examples illustrate the invention.

EXAMPLE 1

(a) Preparation of 3 - phenoxymethyl - coumarilic acid—(Formula IV).

In a 3-litre flask equipped with a stirrer, a vertical condenser and a dropping-funnel, 93.20 g. of phenol (formula V) were dissolved in 270 ml. of methyl ethyl ketone. To this solution were added 1.8 g. of potassium iodide, 2 ml. of dimethylformamide and, while stirring, 136.8 g. of finely ground potassium carbonate. The mixture so obtained was heated under reflux for 30 minutes. Without cooling, a solution consisting of 255 g. of ethyl 3 - bromomethyl - coumarilate (formula IV) in 630 ml. of methyl ethyl ketone was allowed to flow through the dropping-funnel.

The reaction medium was heated under reflux for 6 hours. It was then cooled and the inorganic precipitate filtered off and washed with methyl ethyl ketone.

The organic fractions were collected and the solvent was evaporated to yield 306 g. of an oily residue which was saponified by heating under reflux with a solution of 118.8 g. of 85% potassium hydroxide in 600 ml. of 50% aqueous ethanol.

The resultant solution was cooled and then acidified by means of hydrochloric acid. The precipitate which formed was filtered out, washed over a filter with water and dried in a drying-oven at a temperature of 60°C.

In this manner, 224 g. of 3 - phenoxymethyl - coumarilic acid were obtained (m.p. 194—196°C.; m.p. from isopropanol: 199°C.), which represents a yield of 92.9%.

The following compounds of formula VI were prepared in a manner analogous to that described above by reacting the appropriate

compound of formula IV with the required substituted phenol of formula V.

Compound	Melting point °C.
3 - (3, 5 - methyl - 4 - chloro - phenoxymethyl) - coumarilic acid	210—213
3 - (4 - methyl - phenoxy-methyl) - coumarilic acid	170—172
3 - (4 - chloro - phenoxy-methyl) - coumarilic acid	194—196
3 - (4 - methoxy - phenoxy-methyl) - coumarilic acid	184—185
3 - (4 - methyl - phenoxy-methyl) - 5 - methoxy - coumarilic acid	199—200
3 - (4 - methyl - phenoxy-methyl) - 5 - chloro - coumarilic acid	220—221

(b) Preparation of 6 - oxo - benzo[b]-benzofurano[2, 3 - e]oxepine (Formula II)

In a 10-litre flask equipped with a stirrer and a dropping-funnel, 142 g. of the recrystallised 3 - phenoxy - methyl - coumarilic acid prepared as described in (a) were suspended in 1000 ml. of thionyl chloride containing 2 ml. of dimethylformamide.

The suspension was stirred for 24 hours at a temperature of 20°C., which gave a clear solution. The thionyl chloride was then evaporated under vacuum and the solid residue, comprising 138 g. of 3 - phenoxymethyl - coumarilic acid chloride, was dissolved in 1820 ml. of dichloroethane.

The solution so obtained was poured through the dropping-funnel into a flask to which 255 g. of stannic chloride dissolved in 1820 ml. of dichloroethane had been previously added. During this operation, the temperature was maintained at −5°C., after which it was brought up to between −5 and 0°C. for 1 hour and finally to 20°C. for 20 hours.

At the end of this time, the temperature was reduced and maintained at 0°C., and a 5% aqueous solution of hydrochloric acid was added in order to decompose the organic complex so formed. The organic solution obtained was decanted, washed with water, then with a 2% aqueous solution of potassium carbonate and again with water. The organic fraction was dried over anhydrous sodium sulphate and the solvent was evaporated under vacuum to give 111 g. of crude 6 - oxo - benzo[b]benzofurano[2, 3 - e]oxepine. This crude product was recrystallised in 350 ml. of tetrahydrofuran, which provided a first fraction of 60 g. and a second fraction of 10 g. of pure 6 - oxo - benzo[b]benzofurano[2, 3 - e]oxepine, melting at 152°C. (Yield: 58%).

By using the procedure described above but with different starting products corresponding to formula VI the following compounds of formula II were prepared

Compound	Melting point °C.
8 - methyl - 6 - oxo - benzo-[b]furano[2, 3 - e]oxepine	209—210
8 - chloro - 7, 9 - methyl - 6 - oxo - benzo[b]benzofurano[2, 3 - e]oxepine	264—265
8 - chloro - 6 - oxo - benzo-[b]benzofurano[2, 3 - e]-oxepine	255—257
8 - methoxy - 6 - oxo - benzo-[b]benzofurano[2, 3 - e]-oxepine	143—144
8 - methyl - 6 - oxo - 2 - methoxy - benzo[b]benzofurano[2, 3 - e]oxepine	199
8 - methyl - 6 - oxo - 2 - chloro - benzo[b]benzofurano-[2, 3 - e]oxepine	244

(c) Perparation of 6 - (3 - dimethylamino-propyl) - 6 - hydroxy - benzo[b]-benzofurano[2, 3 - e]oxepine (formula III)

In a 250 ml.-flask equipped with a vertical condenser, a dropping-funnel, a dip thermometer and a stirrer, 1.5 g. of magnesium turnings and a crystal of iodine were heated until vaporization of the iodine and then cooled, after which 20 ml. of dry tetrahydrofuran were added.

The mixture was heated under reflux and a solution of 0.2 g. of ethyl iodide in 5 ml. of dry tetrahydrofuran was allowed to flow into the reaction medium. When the reaction started, a solution of 6.2 g. of γ - dimethylamino - propyl chloride in 20 ml. of dry tetrahydrofuran was added and the mixture so obtained was heated reflux until the complete disappearance of the magnesium turnings. The reaction medium was then cooled in an ice-bath, after which there was added thereto a solution in 45 ml. of tetrahydrofuran of 7 g. of 6 - oxo - benzo[b]benzofurano-[2, 3 - c]oxepine prepared as described in (b).

The reaction mixture was allowed to stand for 20 overs at a temperature of 20°C., and was then poured into a saturated aqueous solution of ammonium chloride maintained at a temperature of 5°C.

The mixture was extracted with ether and the organic portion was washed with water and dried over anhydrous sodium sulphate. After evaporation of the solvent, 9.4 g. of crude product were obtained which, after recrystallisation from isopropanol, provided 6.7 g. of pure 6 - (3 - dimethylaminopropyl) - 6 - hydroxy - benzo[b]benzofurano[2, 3 - e] - oxepine, melting at 160°C. (Yield: 71%).

By following the procedure described above but using the appropriate halogenomagnesium

organic compound and the requisite compound of formula II the oxepines of formula III listed hereunder were prepared:

Compound	Melting point °C.
6 - (3 - piperidinopropyl) - 6 - hydroxy - benzo[b]benzofurano[2, 3 - e]oxepine	162 —163
7, 9 - methyl - 8 - chloro - 6 - (3 - dimethylaminopropyl) - 6 - hydroxy - benzo[b]benzofurano[2, 3 - e]oxepine	168 —169
7, 9 - methyl - 8 - chloro - 6 - (3 - dimethylamino - 2 - methyl - propyl) - 6 - hydroxy - benzo[b]benzofurano[2, 3 - e]oxepine	164 —166
7, 9 - methyl - 8 - chloro - 6 - (3 - piperidino - propyl) - 6 - hydroxy - benzo[b]benzofurano[2, 3 - e]oxepine	110 —111
8 - methyl - 6 - (3 - dimethylaminopropyl) - 6 - hydroxy - benzo[b]benzofurano[2, 3 - e]oexpine	146 —147
8 - methyl - 6 - (3 - dimethylamino - 2 - methyl - propyl) - 6 - hydroxy - benzo[b]benzofurano[2, 3 - e]oxepine	181.5—183
8 - chloro - 6 - (3 - dimethylaminopropyl) - 6 - hydroxy - benzo[b]benzofurano[2, 3 - e]oxepine	153 —154
8 - chloro - 6 - (3 - dimethylamino - 2 - methylpropyl)- 6 - hydroxy - benzo[b]benzofurano[2, 3 - e]oxepine	173 —174
8 - methyl - 6 - (3 - dimethylaminopropyl) - 6 - hydroxy - 2 - methoxy - benzo[b]benzofurano[2, 3 - e]oxepine	151 —152

(d) Preparation of 6 - (3 - dimethylaminopropylidene) - benzo[b]benzofurano[2, 3 - e]oxepine and it fumarate (formula I)

In an Erlenmeyer flask 6.2 g. of 6 - (3 - dimethylaminopropyl) - 6 - hydroxy - benzo[b]benzofurano[2, 3 - e]oxepine prepared as described in (c) were dissolved in 108 ml. of a 10% aqueous solution of sulphuric acid. The solution so obtained was heated to boiling point for 15 minutes. After cooling, 100 ml. of chloroform were added and the solution was made alkaline with a 5% solution of sodium hydroxide. The solution was then extracted with chloroform, washed with water and dried over anhydrous sodium sulphate. The solvent was evaporated and the resulting oily residue composed of 6 - (3 - dimethylaminopropylidene) - benzo[b]benzofurano[2, 3 - e]oxepine was then directly treated with a solution of fumaric acid in isopropanol to give 6.5 g. of 6 - (3 - dimethylaminopropylidene) - benzo[b]benzofurano[2, 3 - e]oxepine fumarate. (Yield: 85%). The fumarate had a melting point of 160°C. when recrystallised from isopropanol.

The oxalate of the same compound has a melting point of 148—151°C.

Following the method described above, the following compounds of formula I were prepared from the appropriate compound of formula III.

Compound	Melting point °C.
8 - chloro - 7, 9 - methyl - 6 - (3 - dimethylaminopropylidene) - benzo[b]benzofurano[2, 3 - e]oxepine	167—170 oxalate
8 - chloro - 6 - (3 - dimethylaminopropylidene) - benzo[b]benzofurano[2, 3 - e]-oxepine	179—180 oxalate
8 - methyl - 6 - (3 - dimethylaminopropylidene) - benzo[b]benzofurano[2, 3 - e]-oxepine	160—162 oxalate
8 - methoxy - 6 - (3 - dimethylaminopropylidene) - benzo[b]benzofurano[2, 3 - e]-oxepine	125—128 oxalate
8 - methyl - 6 - (3 - dimethylaminopropylidene) - 2 - methoxy - benzo[b]benzofurano [2, 3 - e]oxepine	118—122 oxalate
6 - (3 - dimethylamino - 2 - methyl - propylidene) - benzo[b]benzofurano[2, 3 - e]-oxepine	208—210 oxalate
8 - chloro - 7, 9 - methyl - 6 - (3 - dimethylamino - 2 - methyl - propylidene) - benzo[b]benzofurano[2, 3 - e]oxepine	196—197 oxalate
8 - methyl - 6 - (3 - dimethylamino - 2 - methylpropylidene) - benzo[b]benzofurano[2, 3 - e]oxepine	162—163.5 oxalate

Compound	Melting point °C.
6 - (3 - piperidinopropylidene) - benzo[b]-benzofurano[2, 3 - e]oxepine	199—201 oxalate
8 - chloro - 7, 9 - methyl - 6 - (3 - piperidinopropylidene) - benzo[b]benzofurano-[2, 3 - e]oxepine	210—211 oxalate
8 - chloro - 6 - (3 - piperidinopropylidene) - benzo[b]benzofurano[2, 3 - e]oxepine	208—210 oxalate
8 - methyl - 6 - (3 - piperidinopropylidene) - benzo[b]benzofurano[2, 3 - e]oxepine	192—193 oxalate
8 - methoxy - 6 - (3 - piperidinopropylidene) - benzo[b]benzofurano[2, 3 - e]-oxepine	213—214 oxalate
8 - methyl - 6 - (3 - piperidinopropylidene) - 2 - methoxy - benzo[b]benzofurano[2, 3 - e]oxepine	200—202 oxalate
8 - chloro - 7, 9 - methyl - 6 - [2 - (N - methyl - 2 - piperidyl)ethylidene] - benzo-[b]benzofurano[2, 3 - e]oxepine	185—186 oxalate
6 - [(N - methyl - 3 - piperidyl) - methylidene] - benzo[b]benzofurano[2, 3 - e]-oxepine	203—206 oxalate
8 - Methyl - 6 - [(N - methyl - 3 - piperidyl)-methylidene] - benzo[b]benzofurano[2, 3 - e]oxepine	232—234 oxalate
8 - methyl - 6 - [(N - methyl - 3 - piperidyl) - methylidene] - 2 - methoxy - benzo-[b]benzofurano[2, 3 - e]oxepine	245—249 oxalate
6 - [3 - (N - methylpiperazino) - propylidene] - benzo[b]benzofurano[2, 3 - e]-oxepine	246—250 dihydrochloride
8 - chloro - 7, 9 - methyl - 6 - [3 - (N - methylpiperazino) - propylidene] - benzo-[b]benzofurano[2, 3 - e]oxepine	147—249 dihydrochloride
8 - methyl - 6 - [3 - (N - methylpiperazino)-propylidene] - benzo[b]benzofurano[2, 3 - e]oxepine	250—252 dihydrochloride
8 - methyl - 6 - [3 - (N - methylpiperazino) - propylidene] - 2 - methoxy - benzo[b]-benzofurano[2, 3 - e]oxepine	261—263 dihydrochloride
8 - methyl - 6 - [3 - (N - methylpiperazino) - propylidene] - 2 - chloro - benzo[b]-benzofurano[2, 3 - e]oxepine	268—270 dihydrochloride

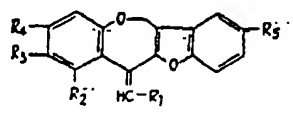
EXAMPLE 2

Tablets were prepared by granulating and compressing the following ingredients in accordance with known pharmaceutical techniques:

Ingredient	Mg. per tablet
6 - (3 - Dimethylaminopropylidene) - benzo[b]benzofurano[2, 3 - e]oxepine fumarate	40
Milk sugar	100
Corn starch	43
Gelatine	5
Alginic acid	4
Talc	6
Silicic acid	1
Magnesium stearate	1
	200 mg.

WHAT WE CLAIM IS:—

1. Benzo[b]benzofurano[2, 3 - e]oxepine derivatives represented by the general formula:



and pharmaceutically acceptable acid addition salts thereof, wherein R_1 represents β - dimethylaminoethyl, β - dimethylaminoisopropyl, β - piperidinoethyl, β - (4 - methylpiperazino) - ethyl, (1 - methyl - 2 - piperidyl) - methyl or 1 - methyl - 3 - piperidyl; R_2 represents hydrogen or methyl; R_3 represents hydrogen, chlorine, methyl or methoxy;

R_4 represents hydrogen or methyl and R_5 represents hydrogen, chlorine or methoxy.

2. 6 - (3 - Dimethylaminopropylidene) - benzo[b]benzofurano[2, 3 - e]oxepine and its pharmaceutically acceptable acid addition salts.

3. 6 - (3 - Piperidinopropylidene) - benzo[b]benzofurano[2, 3 - e]oxepine and its pharmaceutically acceptable acid addition salts.

4. A compound in accordance with the general formula defined in Claim 1 and pharmaceutically acceptable acid addition salts thereof, as described in the foregoing Example 1.

5. A pharmaceutical composition comprising a compound or pharmaceutically acceptable acid addition salt thereof as claimed in Claim 1 in association with a pharmaceutical carrier therefor.

6. A pharmaceutical composition comprising 6 - (3 - dimethylaminopropylidene) - benzo[b]benzofurano[2, 3 - e]oxepine or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutical carrier therefor.

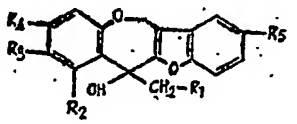
7. A pharmaceutical composition comprising 6 - (3 - piperidinopropylidene) - benzo[b]-benzofurano[2, 3 - e]oxepine or a pharmaceutically acceptable acid addition salt thereof in association with a pharmaceutical carrier therefor.

8. A composition as claimed in Claim 5, 6 or 7, made up in a dosage form adapted for the desired mode of administration.

9. A composition as claimed in Claim 8, wherein the dosage unit is in a form suitable for oral administration.

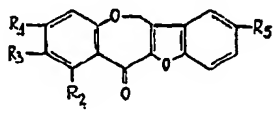
10. A pharmaceutical composition substantially as described in the foregoing Example 2.

11. Process for preparing a benzo[b]benzofurano[2, 3 - e]oxepine derivative in accordance with Claim 1, which comprises reacting a 6 - hydroxy derivative represented by the general formula:



wherein R_1, R_2, R_3, R_4 and R_5 have the same meanings as in Claim 1, with a dehydrating agent to form the required benzo[b]benzofurano[2, 3 - e]oxepine derivative which, if desired, can be reacted with an appropriate organic or inorganic acid to provide the required pharmaceutically acceptable acid addition salt.

12. Process according to Claim 11, wherein the 6 - hydroxy derivative is prepared by reacting in a suitable ether a 6 - oxo - benzo[b]benzofurano[2, 3 - e]oxepine represented by the general formula:



wherein R_2, R_3, R_4 and R_5 have the same meanings as in Claim 1, with a halogenomagnesium organic compound of the general formula:

$$HalMg—CH_2—R_1$$

wherein Hal represents chlorine or bromine and R_1 has the same meaning as in Claim 1, to form a magnesium organic derivative which is hydrolysed to form the required 6 - hydroxy derivative.

13. Process according to Claim 11 or 12, wherein the ether is selected from tetrahydrofuran, diethyl ether, propyl ether, isopropyl ether and butyl ether.

14. Process according to Claim 11, 12 or 13, wherein the dehydrating agent is a strong acid or an inorganic or organic acid chloride.

15. Process according to any one of Claims 11 to 14, wherein R_1 represents β - dimethylaminoethyl and R_2, R_3, R_4 and R_5 all represent hydrogen.

16. Process according to any one of Claims 11 to 14, wherein R_1 represents β - piperidinoethyl and R_2, R_3, R_4 and R_5 all represent hydrogen.

17. Process for preparing a benzo[b]benzofurano[2, 3 - e]oxepine derivative in accordance with Claim 1, substantially as described in the foregoing Example 1.

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